



The Report

The Seventh Advisory Council Meeting of the RIKEN BioResource Research Center

July 3 – 5, 2019



*Foundation for Discoveries
and
Access to the Future*



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(The 1st row, left to right)**

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Dr. Ohkuma, Dr. Murata, Dr. Hayashi, Dr. Ichihashi, Dr. Inoue
(The 2nd row, left to right)**

[Black: AC members / Gray: BRC members]

July 3 – July 5, 2019

**RIKEN BioResource Research Center
and
Okura Frontier Hotel Tsukuba**

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I. The Members List of the RIKEN BioResource Research Center Advisory Council

[International members]

Dr. Martin Hrabě de ANGELIS (Chairperson)

Director, Institute of Experimental Genetics, Helmholtz Zentrum München
German Research Center for Environmental Health (GmbH), Germany

Dr. Kent Lloyd

Professor, School of Veterinary Medicine
University of California, United States of America

Dr. Sean May

Professor, Division of Plant and Crop Sciences, School of Biosciences
University of Nottingham, United Kingdom

Dr. Nadia Rosenthal

Scientific Director, The Jackson Laboratory for Mammalian Genetics
United States of America
(Mail Review)

Dr. Stephen D. M. Brown

Director, Mammalian Genetics Unit, Mouse Genome Centre
Medical Research Council, United Kingdom
(Mail Review)

[Domestic members (Alphabetical order)]

Dr. Masahito Ikawa [Chairperson of Resource Committee of Experimental Animal Division and Review Committee of Experimental Animals (A)]

Professor, Research Institute for Microbial Diseases
Osaka University, Japan

Dr. Tetsuro Mimura [Chairperson of Resource Committee of Experimental Plant Division]

Professor, Department of Biology, Graduate School of Science & Faculty of Science

Kobe University, Japan

Dr. Satoru Miyazaki [Chairperson of Resource Committee of Integrated Bioresource Information Division]

Dean/Professor, Department of Medicinal and Life Sciences

Faculty of Pharmaceutical Sciences

Tokyo University of Science, Japan

Dr. Hiroyuki Ohta [Chairperson of Resource Committee of Microbe Division and Review Committee of Plant-microbe Symbiosis]

Director/Vice President (Education) /Professor, College of Agriculture

Ibaraki University, Japan

Dr. Sumio Sugano [Chairperson of Resource Committee of Gene Engineering Division]

Adjunct Lecturer, Medical Research Institute

Tokyo Medical and Dental University, Japan

Dr. Satoru Takahashi [Chairperson of Review Committee of Experimental Animal (B)]

Professor, Faculty of Medicine

University of Tsukuba, Japan

Dr. Junya Toguchida [Chairperson of Resource Committee of Cell Engineering Division and Review Committee of iPS Cell]

Professor, Institute for Frontier Life and Medical Sciences

Kyoto University, Japan

II. Terms of Reference to the BRAC from the BRC Director

The 7th BRAC is asked to evaluate following item 1 to 4, and to propose ideas and advices for further improvement of the activity of BRC (item 5).

1. Achievements and the 4th Mid-to Long-term Plan of BRC

- (1) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?
- (2) Have the current achievements reached the standards of other major international bioresource centers?
- (3) Is the action plan for the whole BRC in line with the RIKEN's 4th Mid-to Long-term Plan (7 years from FY2018 to FY2024)?
- (4) Is the plan contribute to enhancing the BRC's function in Life Science including Health, Agricultural and Environmental Sciences, and ultimately to returning the benefits of research to society in Japan and the world?

2. SWOT analysis of BRC by the Director

- (1) Is the result of the SWOT analysis valid?
- (2) Are the countermeasures for the result of the SWOT analysis appropriate?

3. International collaboration

- (1) Is BRC conducting the international collaboration actively, and functioning as an international hub?

4. PI assessment

- (1) Is the PI fulfilling the role in line with the BRC's mission?
- (2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?
 - (i) Output and impact
 - (ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories
 - (iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution
- (3) Is the PI appropriately managing and operating the Division/Team?
In addition, does the PI make efforts for training and development of young talent?

5. Advices for further improvement of the activity of BRC

(1) What are R&D and technical innovation that should be commenced immediately (within 2-3 years)?

(2) What are novel resources and new research fields to be developed from a long-term perspective toward the next 5th Mid- to Long-term Plan?

III. Recommendations from BRAC to President Hiroshi Matsumoto

TOR 1

[Achievements and contributions to society]

The BRC has made significant and noteworthy achievements within each of three major missions, operation of Bioresource Infrastructure, Key Technologies Development and Bioresource Frontier Program, thereby significantly contributing to society and the research community both domestically and internationally.

[Consistency with 7-year plan]

Maximization of R&D achievements and improvement in the quality of other operations serves as an overarching theme in RIKEN's 4th Mid-to-Long-term Plan. The BRAC is very confident that the action plan of the BRC is fully in line with the 4th Mid- to Long-term Plan of RIKEN.

TOR 2

[Strengths (internal/positive)]

- Five different bioresources in the same campus in tight collaboration with MEXT-AMED NBRP.
- Collections of unique bioresources developed in Japan.
- High Quality Control: QMS with certification of ISO9001:2015 and quality test by DNA Barcoding etc.
- Research adding value to the bioresources with four new groups under the Frontier Program and one under Infrastructure Division.

[Weaknesses (internal/negative)]

- Limited laboratory management experience of the five recently appointed PIs.
- Shortage of highly qualified and recruitable candidates in Japan to succeed retiring core faculty.
- Imbalance in the diversity within the ranks of scientific faculty, particularly the lack of female PI scientists.

[Opportunities (external/positive)]

- Resources that could be deposited from distinguished Japanese researchers have still remained.
- Easy generation of versatile bioresources by the genome editing technology.

- Recent progress of the precision medicine and agricultural science based on genome information.

[Threats (external/negative)]

- Declining trend of the relative scientific power of Japan, associated with decreased number of researchers in the Life Science, and as consequence resulting in decreased number of resource depositions and requests.
- Unforeseeable and rapid change of research trends that impact the focus for bioresources.

TOR 3

[Collaborations/S&T Hub/Internationalization]

BRC is an active participant in Asian (Asian Network of Research Resource Centers: ANRRC, Asian Mouse Mutagenesis Resource Association: AMMRA) and World networks of bioresource centers (Mouse: IMSR, IMPC; Cell: ISCBI, ICLAC; Plant: MASC; Microbes: WFCC). The BRAC encourages the BRC to continue its special focus on Asian bioresource centers through membership in the ANRRC and other resource-specific organizations including the AMMRA.

TOR 4

[PIs' contribution to the center mission]

Fully aligned and consistent with the overarching RIKEN mission, all PIs of the BRC improve quality of the relevant operations, Bioresource Infrastructure, Key Technology Development and Bioresource Frontier Program, and maximizes their R&D achievements.

[PIs' Performance]

【Research output and impact】

The establishment of the four new research teams has enabled BRC to maintain its leadership position in new and challenging scientific areas. In these ways, the BRC's achievements are significant, long-lasting, and positive contributions to society and to the research community within Japan and overseas.

【Bibliometric analysis】

The scientific value and reputation of BRC resources is evidenced by the high number of requests received over the past 15 years. For example, between 2003 and 2018, the BRC distributed over 255,000 items to nearly 7,200 domestic institutions and approximately 5,400 institutions in 71 countries around the world. In addition, the BRC has contributed

to the publication of over 10,460 papers and the awarding of nearly 1,640 patents.

【Extramural activities/Accomplishments other than R&Ds】

BRC is fostering world-class leaders through a variety of training courses for external scientists, students and technicians, and participation to Tsukuba University Ph.D. Program in Life Science Innovation.

【Other notable findings (optional)】

All PIs of the BRC have demonstrated extreme attention to the highest standards of quality control practices to ensure the rigor, reproducibility, recoverability, and reliability of its resource holdings.

[Laboratory management]

All PIs of the BRC are working appropriately on their own Division/Team management and operation.

[Support for early-career researchers]

All PIs of the BRC are excellent mentors for the early-career researchers, and are committed to helping young talent develop under their care.

IV. The Report

Executive Summary of BioResource Research Center Advisory Council

- Fully aligned and consistent with the overarching RIKEN mission, the BRC improves the quality of operations and maximizes R&D achievements.
- The BRAC applauds the success of Dr. Yuichi Obata in directing and building up the BRC over the last 14 years and in the recruitment of a high-profile excellent research scientist Dr. Toshihiko Shiroishi to serve as the next director.
- All BRC Bioresource Infrastructure Divisions (animal, plant, microbe, cells, gene engineering, IT) provide the highest quality bioresources with guaranteed reproducibility and play a significant role in domestic and international research programs and projects.
- The Key Technology Development Program provides support and services that enhance the scientific value of all BRC activities.
- The BioResource Frontier Program conducts R&D and technology development at the highest level possible and substantially adds value and usability to the bioresources.
- The BRAC applauds the recent reorganization of the BRC which optimizes administration and management of resource infrastructure and enables participation and proactive engagement with new avenues of research.
- Reorganization and integration of the Bioresource Information Division has been wisely implemented and opens opportunities for further growth.

TOR 1. Achievements and the 4th Mid-to Long-term Plan of BRC

(1) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

The BioResource Research Center (BRC) is now in the second year of its 4th Mid-to Long-term Plan (2018-2024) to serve the needs of Japanese society and the domestic and international research community. In that context, the likelihood of the BRC's future success is built upon a solid foundation of past accomplishments. To that end, the number and extent of achievements of the BRC over the past several years were assessed within each of its 3 major missions: 1) the Bioresource Infrastructure Program established to collect, preserve, and distribute high quality, reliable, and cutting-edge bioresources, including experimental mice and plants, human and animal cell lines including induced pluripotential stem (iPS) cells, microorganisms, genetic materials, and information associated with the bioresources, to fulfill societal and research needs promptly, 2) the Key Technology Development Program tasked to develop and improve technologies for preservation of frozen embryos, transportation, rederivation of living animals from frozen germplasm, quality and homogeneity of stems cells, and dissemination of technologies, 3) the Bioresource Frontier Program established to conduct research and development studies to promote the use and application of bioresources to solve scientifically important questions in aging and symbiosis, conquer intractable and age-related diseases, facilitate drug discovery, and increase food production.

Overall, the BRC has made significant and noteworthy achievements within each of these 3 major missions, thereby significantly contributing to society and the research community both domestically and internationally. These achievements, including its extensive collection of scientifically valuable resources, strict attention to the highest QC standards, distribution of world-class research resources, and conducting R&D and technological development to promote active use of bioresources, are particularly noteworthy because they are difficult for individual universities to accomplish. By providing valuable scientific bioresources, the BRC has contributed significantly to raising the efficiency of Japanese and global research activities. For example, the 5 Core operations within the Bioresource Infrastructure Program have met and, in many cases, exceeded expectations in regard to expanding, maintaining, and disseminating its resources, earning the highest evaluation from the 3rd Term of the Ministry of Education, Culture, Sports, Science and Technology (MEXT)-Japan Agency for Medical Research

and Development (AMED) National BioResource Project (NBRP). The bioresources have grown steadily in numbers, quality, and scientific value, including large depositions of human, animal, and microbial cDNAs, over 3,000 microbe strains from the University of Tokyo, and cancer cell lines from the Institute of Development, Aging and Cancer at Tohoku University, and very high-profile depositions of mouse strains, cell lines, and microbes from 4 Japanese Nobel laureates. The international reputation of the BRC is evidenced by the fact that approximately 70% of microbes and related material are deposited from 41 countries. Once deposited, the BRC has demonstrated extreme attention to the highest standards of quality control practices to ensure the rigor, reproducibility, recoverability, and reliability of its resource holdings. The scientific value and reputation of BRC resources is evidenced by the high number of requests received over the past 15 years. For example, between 2003 and 2018, the BRC distributed over 255,000 items to nearly 7,200 domestic institutions and approximately 5,400 institutions in 71 countries around the world. In addition, the BRC has contributed to the publication of over 10,460 papers and the awarding of nearly 1,640 patents. The BRC has concluded multiple comprehensive license agreements for contemporary research tools (e.g., CRISPR/Cas9) and fluorescent proteins (e.g., GFP) to enable its academic users' freedom to operate without fear of infringement of third-party IP rights. In addition, the establishment of the four new research teams have enabled BRC to maintain its leadership position in new and challenging scientific areas. In these ways, the BRC's achievements are significant, long-lasting, and positive contributions to society and to the research community within Japan and overseas.

(2) Have the current achievements reached the standards of other major international bioresource centers?

On many levels, the BRC has implemented operations based on best practices that meet or exceed the standards of other major world-class bioresource centers. For example, when benchmarked against other similar biorepositories, the BRC has the largest collections for human and animal-derived cell lines, second for mouse, plant, and genetic resources, and third in number of depositions for microbes. In addition, the BRC's attention to quality control sets it apart as one of the world's finest bioresources. Like other top bioresources around the world, the BRC's emphasis on quality control practices have significantly reduced the proportion of defects in its resources from 10% to less than 0.01% of its resources. It has also made great strides in protecting its resources from

natural disasters by splitting its cell, mouse, microbe, and plant archives between the main laboratory at Tsukuba and a distant backup facility on the Harima campus. Further, the level of excellence is recognized by its membership and participation in several international organizations, including the International Mouse Phenotyping Consortium (IMPC), the International Stem Cell Bank Initiative (ISCBI), the International Cell Line Authentication Committee (ICLAC), and the Multinational Arabidopsis Steering Committee (MASC). In particular, the BRC has been a major leader in the Western Pacific/East Asia region, serving as a founding member of the Asian Network of Research Resource Centers (ANRRC); former BRC director Yuichi Obata served as ANRRC president from 2011-2016. Finally, the BRC fosters world-class technical and scientific leaders, both through in-house training opportunities and hosting courses and workshops for international trainees from around the world. In summary, the current achievements of the BRC has reached and exceeded the standards of other major international bioresource centers.

(3) Is the action plan for the whole BRC in line with the RIKEN's 4th Mid-to Long-term Plan (7 years from 2018 to 2024)?

Maximization of R&D achievements and improvement in the quality of other operations serves as an overarching theme in RIKEN's 4th Mid-to-Long-term Plan. In this light, the BRC fulfills all requirements as Japan's core center in the area of bioresources. The BRC has taken measures to foresee and react to research trends as well as social needs. The three-tier architecture of BRC's operation has been, and will be, essential for contributing to the aims of the 4th Mid- to Long-term Plan: (1) Development and Operation of Bioresource Infrastructure has ensured the world of first-class operation with respect to usability, associated information, and quality by grasping scientific and social needs. The repositories have and will continue to offer the highest quality material and information to the Japanese research community as well as those outside Japan, which are difficult for individual laboratories or even universities to manage. (2) Development of Key Technologies will advance the preservation, transfer, and usage of bioresources. (3) BRC's active research portfolio within the Bioresource Frontier Program promotes and enriches the bioresource with additional knowledge and value. For this reason, BRC has started four new research teams to lead the development and incorporation of bioresources. This new development is a direct response to the changing landscape in research and societal needs. Along this line the creation and implementation of the new

“Integrated Bioresource Information Division” is highly appraisable and will serve all units of the BRC. In addition, it will ensure to fulfill the mission of the 4th Mid- to Long-term Plan of RIKEN. With all these measures the BRC will contribute to the effective and efficient promotion of cutting-edge research and innovation and to solution of societal needs. Taken together the BRAC is very confident that the action plan of the BRC is fully in line with the 4th Mid- to Long-term Plan of RIKEN.

(4) Does the plan contribute to enhancing the BRC's function in Life Science including Health, Agricultural and Environmental Sciences, and ultimately to returning the benefits of research to society in Japan and the world?

The forward strategy of the BRC lies in several complementary areas, each of which has been convincingly demonstrated in the action plan. The primary function of a resource center is the acquisition of materials and associated data, under appropriate conditions, and the onward distribution of those materials enriched by additional metadata. Careful preservation, curation and a quantifiable quality control of those materials is critical to this process. Underpinning this approach requires internal technical development outputs to ensure relevance of the resources. To promote usage there must be an ongoing integration of existing materials and data, proactively adding value to downstream users. Additionally, it is critical to a perception of the Center and its continued longevity to promote outreach at the research level through publication and patents and more diffusely to the general society.

BRC is clearly a world-leading bioresource center with a strong reputation for providing rapid distribution of high-quality low-cost resources at a very high fidelity. The forward plan expands on these elements without sacrificing those core goals. Several clear strategies are presented in the plan towards significant progression in the Center's mission for health, food, and environmental solutions, as well as complementary development of some novel model systems. The BRC bioresources are not limited to excellent basic science and fundamental research opportunities, but also extend to the development of practical application and translational opportunities. The present plan openly contributes to the advancement of BRC through multiple instances of new technical development, both internally and through collaboration with other institutions that possess similar technology. Given the critical mass of the Center, this provides a high probability for development of novel and unexpected application of technologies. New research teams

have recently been established and substantial infrastructure has been generated and modified to convincingly support this effort moving forwards.

User accessibility to resources alongside enriched accession information is absolutely critical to future development. Data must be connected in a user friendly and supportive manner, both internally with existing databases and with external information sources. To this end, a solid plan for future integration has been strongly presented including a benchmarking and the consultation of other leading resource centers abroad on this matter. The plan also shows suitable attention to user feedback, particularly from clinicians and commercial users. Priorities and strategies for proactive transfer of established technologies to domestic research institutions, together with appropriate training, guidance, and transferable experience in standardization are evident and commendable. The BRC also has a convincing and appropriately broad strategy towards acquiring external funds and participating in international projects.

Finally, the plan includes several areas where educational resources for the Japanese society are explicitly described for future development. This kind of outreach is essential to maintain interest and support for the BRC both from the general public and supporting stakeholders.

TOR 2. SWOT Analysis of BRC by the Director

(1) Is the result of the SWOT analysis valid?

The BRAC finds the BRC Director's SWOT analysis to be appropriate, comprehensive, and valid. The BRAC took the initiative to make additional comments, which are available in the Recommendations from BRAC to President Matsumoto.

(2) Are the countermeasures for the result of the SWOT analysis appropriate?

The BRAC finds that the countermeasures recommended by the Director are appropriate and fully address all items within the SWOT analysis. Further, the countermeasures are fully aligned with the additional comments by the BRAC. The additions to the SWOT analysis that the BRAC has offered might suggest measures for consideration.

TOR 3. International Collaboration

(1) Is BRC conducting the international collaboration actively, and functioning as an international hub?

The BRC is and continues to be fully engaged in international collaborations in many areas, including with regards the sharing of bioresources, the recruitment and training of technicians and scientists, membership and leadership of international societies and organizations, contributions to international standards and best practices, and the international sharing and dissemination of protocols and technologies. For example, over the last several years, the international distribution of physical resources from BRC has ranged from 10% to 30% of total distribution for the different resources. As a result, the rate of foreign use is either stable or increasing over time as a proportion of distribution. In each case where the distribution proportion has increased, the domestic distribution has also increased. In particular, the BRC is actively conducting international collaborations with bioresource centers in Asia, Australia, Europe and America. The BRAC encourages the BRC to continue its special focus on Asian bioresource centers through membership in the Asian Network of Research Resource Centers (ANRRC) and other resource-specific organizations including the Asian Mouse Mutagenesis Resource Association (AMMRA).

The BRC's engagement with the International Mouse Phenotyping Consortium (IMPC) is particularly noteworthy, contributing mice and phenotyping data on more than 70 genes to the global effort to functionally annotate the mammalian genome. The BRC is also actively engaged internationally with its other resources too, cells, plants, and microbes, including the International Stem Cell Banking Initiative (ISCBI), International Cell Line Authentication Committee (ICLAC), the Multinational Arabidopsis Steering Committee (MASC), and the World Federation for Culture Collections (WFCC). Further, the BRC participates internationally in the training and development of young scientists and technicians, such as through the Summer Mouse Workshop involving RIKEN BRC, Nanjing University Model Animal Research Center and Seoul National University. Throughout it all, the BRAC takes notice that BRC is fully compliant to the Convention on Biological Diversity (CBD) and the Nagoya Protocol. Further, promotion of robust and substantial collaboration with Asian countries that have high ratio of young generation and strong economic growth, such as Indonesia, will yield great benefits in the 4th Mid- to Long-term Plan.

In summary, largely due to the extraordinary efforts of the former director, Obata, the BRC is leading several efforts to promote international collaboration more rigorously. The BRAC has no doubt that the new director, Shiroishi will continue to actively engage in international relationships and build on the foundation established before him to ensure the RIKEN BRC solidifies its position as a hub of global interaction and collaboration in the Western Pacific/East Asia.

TOR 4. PI assessment

1: Experimental Animal Division

Division Head: Atsushi Yoshiki

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Dr. Yoshiki leads a Division that has been collecting, performing microbial and genetic QC, and distributing large numbers of high-quality mutant mouse lines for decades. The group also has introduced CRISPR/Cas9 genome-editing tools to accelerate their work and adhere to the demands of the research community. Thus, the PI is fulfilling his role in line with BRC's mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Over the last 6 years, the PI's group successfully collected over 250 mouse lines and distributed about 2,500 items each year. The BRC is recognized as having the 2nd largest collection of mutant mouse lines in the world. The constant contributions to both national and international research communities are well recognized and appreciated.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. By collaborating with companies, the PI's group developed a "Marker Gene Detection Kit" for genetic QC. Originally for internal use, the kit is now commercially available to the research community. Although background purity needs to be examined by SNP analysis, the kit will help decrease the risk of genetic contamination by human

error.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI and his group continue to build on fundamental technologies and their results feed back into their infrastructure. Through domestic collaborations, the PI has developed fluorescent reporter-mouse lines as well as Cre-driver lines. As CRISPR/Cas9 edited mouse strains increase, the group needs to implement a preselection process for new mouse lines because of limited budget and space. Importantly, BRC will benefit from better advertising of their achievements, such as an improved website.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI does an excellent job managing 9 operational groups with about 70 members. The PI and BRC organized an international laboratory-animal network and spent a reasonable amount of effort into training and educating young researchers and technical staff.

2: Experimental Plant Division

Division Head: Masatomo Kobayashi

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The Experimental Plant Division is functioning as an important international center for the established distribution of seeds for *Arabidopsis* and has recently expanded to *Brachypodium* as an alternative experimental plant model for grain species. They distribute various cultured cell lines for both model plants and commercially important species, and hold a large collection of unique molecular genetic resources and vectors. The significance of this center's presence is at a high level of clear international standard. Dr. Kobayashi has been a powerful force in pushing the Plant Division to its current level.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

The preservation and distribution of various Japanese derived germplasm and clonal resources is a significant and unique contribution to Japanese and international research communities. Strict quality control of resources and careful management of data-related

resources by the PI's team meets the world's highest standards of plant resource management. The provision of resources from the Division has led to research results publications in leading journals such as *Nature* and *Science*.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The Division is also active in resource development and research promotion through close collaboration with other research institutions. As a member of the Multinational *Arabidopsis* Steering Committee, they are strengthening collaborations with foreign resource institutions. The Division is becoming the strongest international hub for the Japanese plant science.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The following future plans are appropriate: 1) The construction and maintenance of a web catalogue integrating germplasm data and clonal resources. This will facilitate external user access to resource metadata and allow efficient searching for available materials. 2) The consolidation of resource information and associated metadata for an expanding collection of plant cultured cells. 3) The maintenance and development of new *Brachypodium distachyon* resources.

In addition, the PI is performing proof of concept research into the translational use of *Arabidopsis* research to support crop protection, and they are actively investigating the feasibility of collecting resources for alternative model plant species such as *Marchantia* (bryophyte), and are contributing to internal projects on plant symbiosis. They are also active in public and educational outreach.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI has been making sufficient efforts, and the Division operating smoothly with some staff attaining notable institutional recognition for achievement. Training of young staff with skills necessary for resource preservation is well-promoted and existing staff have been appropriately developed to improved positions.

3: Cell Engineering Division

Division Head: Yukio Nakamura

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. In response to demand from society, the PI has been operating a cell line collection system and rapidly incorporating disease-specific iPS cell lines into BRC's collection. As an ICLAC member, he is continuously aware that preventing cell misidentification through international cooperation is a very important issue. Thus, the PI excels in his efforts towards achieving BRC's mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The number of publications by researchers using the PI's resources is greater than 1,000/year and the number of patents has exceeded 100/year. This demonstrates the Division's constant contributions to all fields of study from basic science to applied research.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The PI is hosting regular training courses on human ES/iPS cells to support domestic research. The PI serves as a member of the Expert Committee of Specified Embryonic Research, a subcommittee of Bioethics and Biosafety organized by the MEXT.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

As an expert in the management and operation of bioresources, the PI is committed to making national guideline policies and deciding future directions.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI is appropriately committed to management and operation of the Division as well as the training and development of young talent. The PI is striving to advance the careers of senior staff and to secure human resources.

4: Microbe Division

Division Head: Moriya Ohkuma

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Based on the numbers of microbes collected and preserved, maintenance of type strains, numbers of distribution and users, the Committee concludes that the PI is fulfilling his role in line with BRC's mission. One of the PI's remarkable contributions is the stimulation of Asian microbiological studies through a positive spiral of microbe deposition, publication, and microbe distribution.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The PI's work contributed to the publication of 3,424 scientific papers and 478 patents by the users between 2013 and 2018.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is a subleader and governing board member of the All-RIKEN cross-center project "Integrated Symbiology (iSYM)", a subleader of the competitive RIKEN Pioneering Project, and the chair of the committee for RIKEN safety and regulation for microorganisms.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI is very active in scientific publication (179, from 2013-2018) and makes himself available for reviewing papers. The PI contributes to the activity of academic societies as the President of the Japan Society of Microbial Resource and Systematics and a board member of the Japan Society of Microbial Ecology.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI is shifting to a group system consisting of multiple individuals, aiming for information sharing and the standardization of roles. The management and operation of the Division is being addressed appropriately. The PI is training and instructing many

postdoctoral researchers and graduate students. The promotion of laboratory staff is also emphasized, and the results of training a diverse range of young talent are highly valuable.

5: Gene Engineering Division

Division Head: Yuichi OBATA, Presenter: Takehide MURATA

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI's work is in line with BRC's mission. High praise should be given regarding the consistently high number of distributed bioresources, >1,200 items every year over the past 6 years. Moreover, the PI is prioritizing metadata enrichment, which will promote active use of the bioresources. Further, the PI is promoting collaboration with other databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) and PubMed to enhance usability.

Identification of resources and confirmation of their authenticity are extremely important for ensuring the resource reliability that forms the basis of the Center's operation. Such QC can only be possible with careful work by devoted staff members, and we would like to express our respect to the PI that he is sincerely and decidedly committed to the QC.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Consolidation of meta-information and sequence information is steadily advancing in the Gene Engineering Division, under the slogan "No information, no bioresources." However, it would be good to see more frequent updates to the analytical results.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is contributing to the goals of his specific mission. Looking forward, there is significant opportunity to expand support for outside researchers and develop new pioneering fields of research. The Committee hopes that the PI will restructure his Division so that research-supporting staff members are fully committed to collecting and maintaining bioresources and that researchers can focus on pioneering new fields which are in line with the mission of the Division.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Information dissemination and public relations activity for the general public, such as the “Tsukuba PhD kids program: science experiment classes” and “lectures for high school students” seem simple, but are actually highly significant activities that not only facilitate understanding and the education of local residents, but also support the foundation of Japan as a nation that values and produces top-level science and technology. We look forward to the BRC’s continuous activities in the realm of social education.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes, the PI is constructing and operating a system that complies with laws pertaining to exports. In terms of training young staff, the PI is actively encouraging the Division’s members to conduct the following activities:

- Participate in lectures for qualification as ISO9001 Quality Management internal auditors
- Survey users’ papers
- Draft brief PR flyers for distribution at academic conferences. Post online articles that introduce specific bioresources
- Participate in major academic conferences

To further develop and pioneer new fields of research in the future, we would like the PI to recruit diverse young staff and actively promote interactions with other Divisions within the BRC.

6: Integrated Bioresource Information Division

Division Head: Hiroshi Masuya

(1) Is the PI fulfilling the role in line with the BRC’s mission?

Yes, the PI is fulfilling his role very well. His Division contributes to the development of original applications, especially the novel mathematical analysis using machine learning and basic technology related to data integration for bioresources. The PI is satisfactorily fulfilling the mission from the perspective of data resources, and he has great potential for the future.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The number of accesses to the BRC website is almost equal to that of the Protein Data Bank Japan (PDBj) and the National Bioinformation Center (NBDC) portal, which are international websites. This indicates that the PI's Division has reached international standards for information dissemination. By participating in IMPC and distributing mouse resources and information, BRC is reaching the standards shared by the major bioresource centers around the world.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the following 4 plans are on-going:

- Data integration of bioresource-related data by ontology
So far, annotations for 91% of the records in the Mouse database and 86% of the records in the microbe database have been completed. For the field of genomic clinical research of rare diseases, the Division has integrated disease information and mouse-phenotypic data using Human Phenotype Ontology and Monarch Disease Ontology. As a result, users are able to search for bioresources by disease name on the BRC website.
- Improvement of the bioresource online catalog database
The Division has developed and maintained a general-purpose data-convention pipeline. Metadata integration, international standardization, and development of a search system across the BRC resources represent major efforts toward the development of the new web catalogue.
- Wider dissemination of bioresource data
By using Resource Description Framework (RDF), the PI is developing an integrated gateway with the iPS portal database in Kyoto Univ, NBDC, and Database Center for Life Science (DBCLS).
- Website renewal
Renewal of the website is underway, which will improve usability via a new graphic user interface. The BRAC recommend domestic and international beta-testers to guide development and implement a feedback loop before launch. Considering customer feedback should be an ongoing process.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The Division has made efforts to conduct Big Data analysis and to develop new visualization technology for bioresource data. The result was comprehensive phenotype-phenotype associations from IMPC data. This is a unique and meaningful way of adding more value to RIKEN BRC resources.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The management and operation of the Division is appropriate, and training of young talent is also being put into practice. The PI is working appropriately to recruit researchers for Big Data analysis. Personnel for metadata integration and data consolidation, as well as annotators and curators, should be employed stably in this Division.

7: Bioresource Engineering Division

Division Head: Atsuo Ogura

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Dr. Ogura has shown strong leadership and under his guidance, the Division has produced highly original and outstanding research in line with the BRC's mission. The newly developed technologies should be advertised and utilized inside and outside BRC.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The Division has developed and improved reproductive bioengineering technologies, including anti-inhibin serum-mediated superovulation, embryo cryopreservation, estrous cycle synchronization via progesterone, and micro-insemination. Further, the group has published 79 papers (2013 to the present) in high-impact journals.

Although scientific impact can be easily recognized by scientists, novel technologies need to be advertised so that they can be used worldwide. Movie clips that explain and demonstrate skilled technologies may help these new and exciting techniques gain recognition.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. As a core part of the BRC, the Division greatly contributed to the development of novel reproductive technologies. Anti-inhibin antibody-mediated super ovulation is just one example.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Their recent genome editing research on hamsters has produced remarkable results that could not have been anticipated from mouse studies. This technology has led to interdisciplinary collaboration with researchers studying hibernation, further joint research with other researchers can be expected. Additionally, high praise should be given for receiving the 5-year Grant-in-Aid for Scientific Research on Innovative Areas for his group to research totipotency.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI appropriately manages the Division and is committed to helping young talent develop under his care. Young researchers in his division have published numerous original papers. Further, they have won competitive funding and awards, advanced their careers with new positions, and are playing active roles in scientific research. We foresee that lab members whom the PI has trained will themselves become PIs in the near future.

8: Technology and Development Team for Mammalian Genome Dynamics

Team Leader: Kuniya Abe

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI continues to successfully fulfil his role in line with the BRC mission by producing novel EpiSCs and developing technology for analyzing how stem cells transition from naïve to primed. In addition, the PI has established CRISPRi and CRISPRa expressing iPS cells, which are a useful resource for researchers in Japan and around the world.

(2) Do the PI's achievements in R&D reach the international standard in light of the

following three aspects?

(i) Output and impact

Yes, the PI's achievements in research and development have met high international standards. This is evidenced by the publishing of a number of original papers regarding new resources and established methods.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the Team has disseminated their research, collaborated within RIKEN, and acquired several intellectual property rights. In particular, the Dox inducible CRISPRi/a system will add additional value to the existing cell lines and the BRC.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes, the Team is developing a new non-invasive method for epigenome dynamics sensing, which has allowed them to find a 3rd type of pluripotent stem cell, non-naïve but not primed. These research projects have the potential for achieving international prominence.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes, The PI is appropriately handling the management and operation of his Team. The PI is an excellent mentor for his Team, in addition to the promotions received by his research trainees, he has taken on the training and education of graduate students, including those from outside Japan.

**9: Technology and Development Team for Mouse Phenotype Analysis
Team Leader: Masaru Tamura**

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, considering the PI's participation in the IMPC, his activity is in line with the BRC's mission. Additionally, he is contributing to the BRC's mission by directing the development of novel research methods, including X-ray micro-CT technology and contrast agents.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The Team has conducted high quality joint international research that has led to publications in high-impact international journals. The Team's output and impact are satisfying international standards.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the Team is focusing on phenotyping and has effectively collaborated with other laboratories. In addition, they have provided their platform to the Japan Mouse Clinic services and participated in collaborations with researchers inside and outside of RIKEN.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Micro-CT analysis method that provides a new level of embryo phenotyping analysis. In addition, the Team is striving to establish a new telemetry-analyzing technique that will greatly help in the efficient and automated analysis of phenotyping. Implementing this new telemetry system using AI-based analysis will lead the next generation animal phenotyping analysis.

To this end, close linkage with the Integrated BioResource Information Division will be very important, because formidable AI technologies are now developed. It may be synergistic to develop joint appointments between the Team and the Integrated BioResource Information Division.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. Initially, this Team lacked a sufficient number of researchers who were able to conduct phenotyping of large numbers of mice. However, after great effort, the PI was able to recruit young talent for the Team. The PI is appropriately managing the Team. The Team will be strengthened even more if they were able to recruit informaticians.

10: iPSC-based Drug Discovery and Development Team

Team Leader: Haruhisa Inoue

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI is formulating and carrying out research and development strategies leading to the use of disease-specific iPS cells held by BRC in the drug discovery field. Thus, the PI is playing an important role in accordance with the mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Publication of original articles in high-impact factor (IF) journals is proceeding steadily for each individual topic. The PI is promoting research at a high international standard.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. At the BRC satellite Keihanna laboratory, the PI is fulfilling his own mission to promote the utilization of disease-specific iPS cells. In addition, by hosting international symposia, the PI has actively promoted collaboration and social contributions both in Japan and overseas.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The PI promotes collaboration with industry in order to utilize the disease-specific iPS cells, providing not only cells, but also methods for evaluation. Additionally, these efforts promote collaboration and social contributions both in Japan and overseas.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI is working to manage and operate the Teams appropriately. Development of young talent will be an issue in the future.

11: iPS Cell Advanced Characterization and Development Team

Team Leader: Yohei Hayashi

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI is conducting challenging research aimed at technological developments that will yield unique outcomes. At the same time, it is important to balance this activity with his commitment to developing bioresource infrastructure.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

As a young researcher, the PI's previous achievements are noteworthy and some of them have already had great impact.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The proposed research direction closely follows BRC's mission, and the Team is expected to make significant contributions in the near future.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Introducing laser technology as a new methodology for characterizing iPS cells is a unique project. Production of reporter-iPS cell lines should be performed with focus on good communication with research community.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI has newly established his laboratory and is appropriately tackling the management and operations of his Team. The PI is also committed to training and development of young talent.

12: Next Generation Human Disease Model Team

Team Leader: Takanori Amano

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI has only just begun his current position. However, he understands the BRC's mission well and is setting forth appropriately aligned research plans.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

It is too early to say, but his plans will likely be fruitful. At his former post, the PI built a solid track record of research into the control of gene expression. The PI's notion that studying the function of non-coding variants is necessary for a comprehensive understanding of the causes of human disease is important for the disease research community.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. Based on social needs, the PI selected Alzheimer's disease, frontotemporal lobar degeneration, Hirschsprung's disease, and branchio-oto-renal syndrome as target diseases for study. The Team has begun generating human-disease models by introducing point mutations using CRISPR/Cas9 genome-editing technology. With the aim to achieve optimized precision medicine, the Team has already begun joint research projects with researchers and clinicians who specialize in disease-genome analysis.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The PI is working on understanding genetic context of difference in penetrance of mutant phenotype by comparison of the phenotype on the two genetic backgrounds of B6 and JF1 and on clarifying relevant *cis*-regulatory variations and gene-regulatory networks using RNA-seq of F1-hybrid mice. This is thought to be a challenging but important project for developing a better understanding of human diseases, but it will need careful assessment when set against the priorities of generating and analyzing key models of disease variants.

Generation of real disease models and subsequent research need to be based on the demand from the clinical research community.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

As the PI has just been appointed, selection of staff for the generation of mouse models and phenotype analysis are now in process. The Council trusts that appropriate personnel will be brought on board and trained.

13: Plant-Microbe Symbiosis Research Development Team

Team Leader: Yasunori Ichihashi

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI is playing a role in accordance with BRC's mission. The PI is developing novel technology to use arbuscular mycorrhizal fungi (AMF) resources, as well as establishing a model system for the study of plant-microbe symbiosis. Such efforts are viewed as fulfilling his role well. The Team is already advancing the *in vitro* propagation of AMF. In the future, we anticipate the development, storage, provision, and characterization of novel resources.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Adopting the national research project “Cross-ministerial Strategic Innovation Promotion Program (SIP)”, supported by the Japanese Cabinet Office, as a primary research project is commendable. Additionally, the PI published a co-authored review of plant-microbe symbiosis in *Nature Plants*, with high international impact.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is participating in RIKEN's internal cross-sectional program, iSYM. Further increase of research results is expected in the future.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI is actively addressing integration of different research fields, including plant science, agricultural science, microbiology, and informatics. The PI established a

foundation for conducting strategic research, e.g., field omics analysis and the screening of uncultured microbes using microdroplet technology. The PI is now progressing with the acquisition of an external budget to form the foundation for implementing their plan. The PI is also planning to apply IP to contribute to the novel use of breath-capture technology and pursue patenting. Additionally, the PI contributes appropriately to outreach activities, such as the Tsukuba City Future Creation Conference.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI is working appropriately on team management and operation. He is also making efforts to develop young talent. Despite a broad range of planned research projects, the PI is utilizing the latest information systems to create smooth communication within the Team, and has consistently conducted excellent management and operations. The PI has also received large external funds, such as the SIP (FY2018-FY2023). Although the Team is still in its inaugural year, the Team members, including young researchers and research assistants, seem to be working well. Young members should be mentored to ensure that they produce results relevant to the research Team. In addition to developing a laboratory comprising mainly young members, the PI is also making efforts to train a visiting researcher from a private company and a visiting student from a university.

TOR 5. Advice for further improvement of the activity of BRC

(1) What are R&Ds and technical innovation that should be commenced immediately (within 2-3 years).

- Reinforcing R&D for functional genomics (e.g., single cell genomics), phenotyping (e.g., pathophysiology), data analysis, enhancing the collection, integration, dissemination of genomic, phenotypic data and information on existing bioresources.
- Consider best practices that enable precise identification of genomic information.
- Capitalize on model plants resources for genome editing, gene modification, and other manipulation.
- Adopt the Findable Accessible Interoperable and Reusable (FAIR) Data Principles.

- Adopt internationally-recognized systems (e.g., Research Resource Identifier, RRID) for all appropriate bioresources, protocols, and reagents.
- Establish a process for regular and remote offsite data backup (e.g., tape drives, cloud storage, etc.).
- Develop the infrastructure necessary for integrating all bioresource-related data and to make it minable, searchable, and browsable to enhance its utilization and dissemination.
- Establish multiple routes for regular feedback from the user community (e.g., formally established user groups, user surveys, webinars, etc.).
- Undergo a strategic planning process to understand global research trends that could inform new ways to utilize the resource and increase distribution both domestically and internationally.

In addition:

- Discuss with the appropriate RIKEN leadership how to increase recruitment of more female scientists as principal investigators, group leaders and junior faculty. In particular, improvement of gender imbalance should be urgent task.
- Consider recruiting, hiring, or collaborating with a qualified mouse pathologist.
- Consider establishing limited, customized sequencing services available on-campus.

(2) What are novel resources and new research fields to be developed from a long-term perspective toward the 5th Mid-to-Long-term Plan?

- A new program on Big Data analysis is an important development, in particular the integration of machine learning (ML) as a tool for the analysis of rich, complex data. One area that will be important for the future is to ensure that Big Data developments at BRC are enriched by cross-talk to large high dimensional datasets from Biobanks and Rare Disease datasets, in Japan and potentially further afield. A relevant option is to accelerate development of phenotyping platforms based on the ML technology, and strive to recruit, hire, and/or establish formal collaboration with a critical mass of bioinformaticians with expertise in the AI and ML technologies and Statistical Mathematics that can be applicable to Life Science.
- The BRAC recognizes the indisputable value of *in vivo* models, especially mice, to inform functional knowledge of the genome. For example, *in vivo* functional

analysis of human orthologs in the mouse genome is crucial to the success of translational research that can be relevant to society.

- Investigate utility of pursuing accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care.
- Develop QC control for genetic drift caused by accumulation of spontaneous mutations in live stocks. It is particularly important for many inbred strains derived from wild mice, which are unique to RIKEN BRC.
- Perform a self-review and audit to determine if barrier to access to BRC bioresources exist, either through slow response times, high costs, limited awareness, ineffective communication or outreach, poor technical or customer service, restrictive MTA's or IP issues, etc.

Other options to be considered:

- Comparative genomics of bioresources with natural diversity
- Investigation of complex traits and quantitative traits and development of new mouse resources for these fields
- 4-D phenotyping that produces time-series data of morphology, physiology, and behavior
- Upgrade and expansion of existing physiological screening technologies with next generation non-invasive screening devices
- Development of currently unavailable tools for high throughput customized phenotype screening
- Investigation of non-coding regulatory elements and relevant mutations
- Projects to more thoroughly investigate modulators of gene expression

References